Case Report

Successful treatment of carcinomatous meningitis with erlotinib and whole brain radiotherapy

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Abstract

Carcinomatous meningitis (CM) is a severe complication of lung cancer. Here, we report on two *EGFR*-mutated patients who attained relatively long survivals by erlotinib treatment after diagnosis of CM. The first case is a 59-year-old woman who was diagnosed as adenocarcinoma harboring an *EGFR* mutation (L858R); her disease was at stage IV with multiple brain metastases. The time from the initial diagnosis of lung cancer to CM was 364 days. Erlotinib was administered for 5 months, and the survival time from the diagnosis of CM was 278 days. The second case is a 60-year-old man who underwent right lower lobe lobectomy and was diagnosed as adenocarcinoma with an *EGFR* mutation (E746-750 deletion) and at the pathological stage IIA (pT1N2M0). Later, the disease was recurring as brain metastasis, and progressed to CM 637 days after diagnosis of lung cancer. Erlotinib was administered for 5.5 months, and the survival time from the diagnosis of CM was 281 days. These cases indicate that erlotinib is a reasonable option for the treatment of CM in *EGFR*-mutated patients.

Key Words: *EGFR* mutation, carcinomatous meningitis, erlotinib, whole brain radiotherapy

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Introduction

Carcinomatous meningitis (CM) is a severe complication of lung cancer. The frequency of CM in solid tumors is approximately 5-10%, which has gradually been increasing^{1, 2, 3)}, with lung and breast cancer being the most common primary malignancies⁴⁾. The treatment of CM in advanced non-small cell lung cancer (NSCLC) is not satisfactory because there is no standard treatment for CM available and there is limited survival; the median survival ranges from 4 to 9 weeks^{5, 6)}.

However, recent reports have described good responses in NSCLC patients with epidermal growth factor receptor (*EGFR*) mutations, treated with *EGFR*-tyrosine kinase inhibitors (TKIs). Gefitinib was the first TKI that was shown to provide dramatic responses in those patients. Nevertheless, after a median period of about 10 months⁷⁾, the disease in the majority of the patients eventually progressed. The brain is a common metastatic site

of NSCLC, and it is similar after using gefitinib. Though erlotinib is also an *EGFR* TKI with an activity similar to that of gefitinib, some reports have shown that erlotinib is a reasonable option for the treatment of brain metastasis and CM⁸⁾.

Here, we report on two cases that attained relatively long survivals after the diagnosis of CM.

Case presentation

The first case is a 59-year-old woman, who had never smoked, who suffered from back pain and numbness in the left little finger. Chest X ray and a computed tomography (CT) scan revealed right pulmonary nodules. Magnetic resonance imaging (MRI) of the brain showed multiple brain metastases. A pathological diagnosis of adenocarcinoma with an *EGFR* mutation (L858R) was established by transbronchial biopsy. The patient's staging was IV with multiple brain metastases as well as bone metastasis (Fig. 1).

She received gefitinib for 11 months, 250 mg/day for the first 39 days, then every other day because of liver dysfunction. And whole brain radiotherapy (total 30Gy: 3Gy/fraction) was done from the day following the di-

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agnosis. Then, radiotherapy for bone metastasis was administered, and zoledroic acid was injected. She continued to take gefitinib for a total of 12 months, at which point the progression of her disease was diagnosed. Her chest CT scan revealed an increase in the size of a pulmonary nodule. PET showed bone metastasis of a new

lesion. Subsequent brain MRI revealed diffuse leptomeningeal disease prominent in the cerebellum, which was diagnosed as CM (Fig. 2). She received 1 cycle of a combination chemotherapy consisting of carboplatin and paclitaxel, but, because of side effects, we had to change the treatment to erlotinib, which made CM a stable dis-

Fig. 1. Images of case 1 when diagnosing lung cancer
 A: Chest X-ray showed a nodular shadow at a hilus in the right lung.
 B: CT scan revealed a nodular shadow with spicula formation and hilar lymph node swelling.
 C: Gadolinium-enhanced T1-weighted brain image showed multiple brain metastases.

Fig. 2. Brain MRI images of Case 1 after CM
 A: Gadolinium-enhanced T1-weighted brain image revealed pia-subarachnoid space enhancement invaginating into the sulci of the cerebellum, indicating carcinomatous meningitis.
 B: Gadolinium-enhanced T1-weighted brain image after 2 months of erlotinib treatment showed partial response of the brain metastases and the leptomeninges.

ease without acute progression. Erlotinib was continued for 5 months. The time from the initial diagnosis of lung cancer to CM was 364 days, and the survival time from the diagnosis of CM was 278 days.

The second case is a 60-year-old man who smoked 800 pack-years and presented with abnormality on a chest X ray in a health examination at his company. Chest X ray and CT scan revealed a pulmonary nodule in the right lung. No metastasis was found, and the staging was Stage Ib (cT2N0M0) (Fig. 3). A right lower lobe lobectomy was done, and the final diagnosis and pathological staging were adenocarcinoma with *EGFR* mutation (E746-750 deletion) and Stage IIA (pT1N2M0). As an adjuvant therapy, he received chemotherapy consisting of carboplatin and docetaxel, concurrent with radiotherapy of the mediastinum (total 60Gy, 2Gy/fraction). After radiotherapy, the chemotherapy was stopped after 2 cycles because the patient had developed irradiation pneumonitis.

At 13 months from the diagnosis of lung cancer, brain MRI revealed multiple brain metastases. He then received gefitinib 250 mg/day for 5 months, then every other day for 3 months because of side effects in the skin. At 18 months after the initial diagnosis, he presented with nausea, disorientation and diplopia. Subsequent brain MRI revealed high intensity signals in sulcus of the cerebellum, which showed CM (Fig. 4). He received whole brain radiotherapy (total 30Gy, 3Gy/fraction) and erlotinib 150 mg/day for 2 weeks, and then received erlotinib 100 mg/day for 4 months because of nausea and diarrhea. At 23 months, the disease was progressing with ascites and peritoneal metastasis, and we changed erlotinib to pemetrexed, 3 cycles. He subsequently received erlotinib again for 1 month. The time from diagnosis of lung cancer to CM was 637 days, and the survival time from the diagnosis of CM was 281 days.

Discussion

From 2007 to 2012, a total of 2,190 patients with NSCLC were treated in our institution, and there were 8 patients with CM (Table 1). Of the 8 patients with CM, there were 5 patients with *EGFR* mutations, none of whom had the T790M second mutation at the diagnosis of CM. One, two, and two patients were treated by erlotinib, gefitinib, and both, respectively, before diagnosis of CM (Table 2). Only the two patients, who had received gefitinib before diagnosis of CM were treated by erlotinib after diagnosis of CM. These two patients had relatively long survival times after diagnosis of CM.

The prognosis of patients with CM associated with lung cancer is still very poor. But there are case reports on gefitinib and erlotinib being effective on metastatic lesions in the central nervous system. Our two patients received gefitinib before being diagnosed with CM, and

after the CM diagnosis they received erlotinib (Table 2). Whole brain radiotherapy was combined with erlotinib when they were diagnosed with brain metastases.

There are several reports published on disease control in connection with erlotinib administration after gefitinib treatment, with response rates ranging from 9.5-14%^{9, 10}. But if the patients have never been treated by erlotinib when CM is diagnosed, erlotinib is an option to control CM. Thus, animal studies have revealed that the blood brain barrier (BBB) hinders the delivery of gefitinib to tumor cells in the central nervous system (CNS). Therefore, the tumor cells in the CNS would not become tolerant to TKI because of administration of gefitinib and remain sensitive to erlotinib, which penetrates the BBB to some extent because of its relatively higher serum con-

Table 1: Meningitis patients' characteristics (n=8)

Median age (range)	64 (57-72)	
Gender		
	Male	5
	Female	3
Pathology		
	Adenocarcinoma	5
	BAC, Adenocarcinoma	1
	Squamous cell carcinoma	1
	Unknown	1
EGFR gene status		
	Mutant	5
	Wild-type	1
	Unknown	2
Initial Stage (at LC diagnosis)		
	II	1
	III	1
	IV	6
Initial PS (at LC diagnosis)		
	0-1	4
	2	1
	3	1
	4	1
Brain metastasis before CM diagnosis	Yes/No	3 / 5
after CM diagnosis	Yes/No	7 / 1
Diagnosis of CM by		
	MRI	4
	Cytology	0
	MRI/Cytology	4
Days from diagnosis from LC to CM		
	Median (range)	874 (4-2239)
Treatment prior to diagnosis of CM		
	Radiotherapy	
	Cyber knife	1
	WBRT	4
	EGFR-TKI	
	Gefitinib	2
	Erlotinib	1
	Both	2

Table 2: Time of TKI (gefitinib, erlotinib)

TKI before CM	TKI after CM	number
Gefitinib	-	2
Erlotinib	-	1
Gefitinib and Erlotinib	-	2
Gefitinib	Erlotinib	2
Gefitinib	Gefitinib	1
		total 8

Fig. 3. Images of case 1 when diagnosing lung cancer
A: Chest X-ray showed a pulmonary nodule in the right lung.
B: CT scan showed a pulmonary nodule in the right lower lobe.
C: Gadolinium-enhanced T1-weighted image indicated no brain metastasis.

Fig. 4. Brain MRI images of Case 2 after CM
A: Gadolinium-enhanced T1-weighted brain image revealed high intensity signals in sulcus of the cerebellum, indicating carcinomatous meningitis.
B: Gadolinium-enhanced T1-weighted brain image after whole brain radiotherapy and erlotinib treatment for 2 months showed partial response of the intensive signal of the leptomeninges.

centration compared with that of gefitinib¹¹⁾.

Radiotherapy for CM was reported to be both feasible and effective in relieving symptoms^{1, 12)}, although some reports found that whole brain radiotherapy for CM in patients with NSCLC did not prolong survival^{13, 14)}. In our two cases, whole brain radiotherapy was administered when brain metastasis was revealed, but before CM was diagnosed. And to improve the CM patients with lung cancer, EGFR-TKI treatment, especially erlotinib, combined with radiotherapy of the brain may be a therapeutic approach. Further studies and reports are needed in order to clarify the effect and the timing of radiotherapy to the brain in regard to the kinetics of EGFR-TKI.

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